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Minireview

Programmed cell death triggered by nucleotide pool damage and its prevention by MutT homolog-1 (MTH1) with oxidized purine nucleoside triphosphatase

Yusaku Nakabeppu*, Sugako Oka, Zijing Sheng, Daisuke Tsuchimoto, Kunihiko Sakumi

Division of Neurofunctional Genomics, Department of Immunobiology and Neuroscience, Medical Institute of Bioregulation, Kyushu University 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

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ABSTRACT

Accumulation of oxidized bases such as 8-oxoguanine in either nuclear or mitochondrial DNA triggers various cellular dysfunctions including mutagenesis, and programmed cell death or senescence. Recent studies have revealed that oxidized nucleoside triphosphates such as 8-oxo-dGTP in the nucleotide pool are the main source of oxidized bases accumulating in the DNA of cells under oxidative stress. To counteract such deleterious effects of nucleotide pool damage, mammalian cells possess MutT homolog-1 (MTH1) with oxidized purine nucleoside triphosphatase and related enzymes, thus minimizing the accumulation of oxidized bases in cellular DNA. Depletion or increased expression of the MTH1 protein have revealed its significant roles in avoiding programmed cell death or senescence as well as mutagenesis, and accumulating evidences indicate that MTH1 is involved in suppression of degenerative disorders such as neurodegeneration.

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1. Introduction

Cellular components such as lipids, proteins and nucleic acids are at high risk of being oxidized by reactive oxygen species (ROS). ROS are inevitable byproducts of electron transport in the mitochondria or other normal metabolic pathways and are also generated as useful products for various biological processes such as host defense, neurotransmission, vasodilation and signal transduction. Their production is markedly enhanced by various environmental exposures. Such oxidative damage is considered to be a major cause for various types of cellular dysfunction resulting in cell death or mutagenesis, which may in turn cause degenerative disorders and neoplasms [1].

Organisms are equipped with defense mechanisms to minimize the accumulation of ROS. For example, superoxide dismutases convert superoxide to oxygen and hydrogen peroxide and the latter is further detoxified by peroxidases or catalases. Mice lacking the *SOD2* gene encoding mitochondrial superoxide dismutase have severe abnormalities in development and growth, including cardiomyopathy and neurodegeneration [2]. Once excessive ROS

Abbreviations: 8-oxoG, 8-oxoguanine; 8-oxo-dGTP, 8-oxo-2′-deoxyguanosine triphosphate; 2-OH-A, 2-hydroxyadenine; 2-OH-dATP, 2-hydroxy-2′-deoxyadenosine triphosphate; AIF, apoptosis-inducing factor; BER, base excision repair; NO, nitric oxide; PARP, poly(ADP-ribose) polymerase; ROS, reactive oxygen species; SOD, superoxide dismutase; SSBs, single strand breaks.

* Corresponding author. Tel.: +81 92 642 6800; fax: +81 92 642 6791.
E-mail address: yusaku@bioreg.kyushu-u.ac.jp (Y. Nakabeppu).

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accumulates in the cells, these cells can no longer avoid severe oxidative damage. Even in the presence of functional superoxide dismutases, accumulation of oxidized macromolecules in human tissues gradually occurs during normal aging; hence, oxidative damage has been implicated in aging and degenerative disorders and may well be the major cause of these disorders [1].

Among the various types of oxidative damage to cellular macromolecules, damage to nucleic acids is particularly hazardous because of the genetic information present in cellular DNAs (nuclear and mitochondrial), can be altered. Furthermore, oxidized nucleotides can disturb various cellular processes. Such oxidative damage accumulating in cells often results not only in mutagenesis, but also in programmed cell death. The former can initiate carcinogenesis in somatic cells, and mutations fixed in germ lines cause genetic polymorphisms or cause hereditary diseases with a malfunction of the gene(s), while the latter often causes degenerative diseases [3–6].

There are two pathways for the accumulation of oxidized bases in cellular DNA or RNA: one is a result of the incorporation of oxidized nucleotides generated in nucleotide pools while the other is a result of the direct oxidation of bases in DNA or RNA [7]. Recent progress in studies of the sanitization of nucleotide pools, as well as DNA repair, has revealed that the impact of oxidation of free nucleotides is unexpectedly large, in comparison with the direct oxidation of DNA [8]. In this review, we focus on the programmed cell death induced when oxidized purine nucleoside triphosphates are accumulated in the nucleotide pools and how their sanitizing enzyme MTH1 prevents such biological consequence.

2. Oxidation of purine nucleotides and their incorporation into cellular DNA

Among the nucleobases, guanine is known to be the most susceptible to oxidation and its simple oxidized form, 8-oxoguanine (8-oxoG), is one of the major oxidation products in DNA or nucleotides [9]. *In vitro* exposure of the guanine base to H_2O_2 and ascorbic acid or to $Fe(II)^-$-EDTA generates 8–9 times more 8-oxoG residues in the nucleotide dGTP than in DNA. Interestingly, the C-8 position of dATP is not oxidized in the treatments; instead, the C-2 position of dATP is oxidized, thus yielding 2-hydroxy-2′-deoxyadenosine triphosphate (2-OH-dATP). However, treatment with $Fe(II)^-$-EDTA generates 2-hydroxyadenine (2-OH-A) residues in DNA to as little as 1.5% of the level of 2-OH-A residues that are formed from dATP [10]. Free nucleotides are thus more susceptible to oxidation by ROS than is DNA.

These *in vitro* studies indicated that dGTP is likely to be most susceptible to oxidation by *in vivo* generated ROS, thus generating 8-oxo-dGTP. Although there have been few reports measuring the *in vivo* concentration of 8-oxo-dGTP in the nucleotide pool, it has recently been reported that 8-oxo-dGTP is present at 0.2–2 μM range in the mitochondrial dNTP pools of several rat tissues under normal conditions [11].

It has been established that 8-oxo-dGTP and 2-OH-dATP are frequently misinserted opposite template adenine or guanine, respectively, in DNA by various DNA polymerases for bacterial genomes, and in the nuclear and mitochondrial DNA in mammals, because of their altered base pairing properties [11–18] (Fig. 1A). 8-OxoG pairs with adenine and cytosine at equal efficiency because it prefers the *syn*-form compared with guanine, which takes mostly an *anti*-form and exclusively pairs with cytosine. However, 2-OH-A also can pair with guanine in a *syn*-form in addition to thymine. It has been shown that these oxidized nucleotides indeed increased certain mutations when they were introduced into *Escherichia coli* or mammalian cells [19,20].

As summarized in Fig. 1B, 8-oxo-dGTP is misinserted opposite template adenine as well as cytosine in DNA, thus causing mainly an A:T to C:G transversion mutation after two rounds of replication. 2-OH-dATP tends to be misinserted opposite guanine mostly, thus inducing mainly G:C to T:A transversion mutation.

3. MTH1 is a major oxidized purine nucleoside triphosphatase in mammals

E. coli mutT mutants exhibit the strongest mutator phenotype among all known *E. coli* mutator mutants and the spontaneous occurrence of A:T to C:G transversion mutation increases 1000-fold compared with wild-type. Maki and Sekiguchi demonstrated that the MutT protein hydrolyzes 8-oxo-dGTP to 8-oxo-dGMP and pyrophosphate, thus sanitizing the nucleotide pool [12]. The MutT protein also efficiently hydrolyzes 8-oxo-GTP and *mutT* mutants accumulate 8-oxoG in DNA and mRNA; 8-oxoG in the latter also results in the production of mutant proteins [21]. The *E. coli* Orf135 protein hydrolyzes 2-OH-dATP [22] and its mutants exhibit a 2-fold increase in the spontaneous occurrence of A:T to C:G transversion. The introduction of 2-OH-dATP, but not 8-oxo-dGTP or other nucleotides, into Orf135 mutants, specifically increases the mutation frequency compared with wild-type [23]. MutT and Orf135 proteins share the nudix (nucleoside diphosphate linked moiety X) motif corresponding to the 23 residues from Gly37 to Gly59 of *E. coli* MutT, which constitute the phosphohydrolase module for hydrolysis of phosphate bonds of the substrates [24,25].

We have identified a human homolog of the MutT protein and designated it as MTH1 (MutT homolog-1) [26–28]. However, it is now referred to as NUDT1 because it is the first identified protein with the nudix motif in eukaryotes. In contrast to MutT, MTH1 efficiently hydrolyzes two forms of oxidized dATP, 2-OH-dATP and 8-oxo-dATP, as well as 8-oxo-dGTP. It also hydrolyzes the corresponding ribonucleotides, 2-OH-ATP, 8-oxo-GTP and 8-oxo-ATP. Among these, MTH1 has the highest affinity to 2-OH-ATP (K_m = 4.3 μM), while the highest catalytic efficiency was observed in 2-OH-dATP ($k_{cat}/K_m = 1.68\ s^{-1}\ \mu M^{-1}$) [29,30]. We determined the solution structure of MTH1 by multi-dimensional heteronuclear NMR spectroscopy [31]. The protein adopts a highly similar folding pattern to *E. coli* MutT, despite the low sequence similarity outside the conserved nudix motif [32]. The substrate binding pockets are dissimilar, which might account for the different substrate specificities observed for the two enzymes [33]. Based on the arrangement of the pocket-forming residues, combined with the mutagenesis data, we generated models for the substrate recognition of MTH1 in which Asn-33 and Asp-119 play pivotal roles in discriminating the oxidized form of the purine, namely 8-oxoG and 2-OH-A, while Trp-117 is important for determining the affinity with purine rings [34,35]. Among known proteins with the nudix motif, two other mammalian proteins, MTH2 (NUDT15) and NUDT5, were identified with the potential to hydrolyze either 8-oxo-dGTP or 8-oxo-(d)GDP to 8-oxo-(d)GMP, respectively [36–38]. NUDT5 also hydrolyzes 8-oxo-dADP and to a lesser extent 2-OH-dADP [39]. The discovery of NUDT5 with 8-oxo-(d)GDPase activity, further revealed that MTH1 and MutT can both hydrolyze 8-oxo-GDP [38,40]. MTH1 also recognizes oxidized forms of dATP and ATP as mentioned above. Therefore, we expect that their diphosphate forms can be hydrolyzed by MTH1, suggesting that MTH1 is the most powerful enzyme for the sanitization of nucleotide pools [8] (Fig. 1B). Gene knockdown experiments for MTH1, MTH2 and NUDT5 in cultured human cells revealed that MTH1 deficiency induced an increased occurrence of A:T to C:G transversion mutations when 8-oxo-dGTP was introduced into cells [41].

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